

Glutethimide and circulating 1,25-dihydroxyvitamin D in vitamin D intoxication

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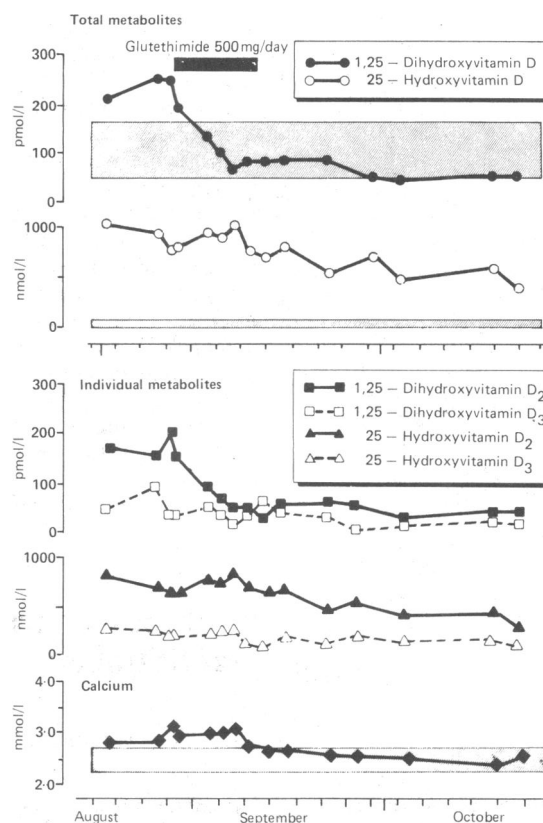
Iqbal and Taylor used glutethimide to treat a patient with vitamin D₂ intoxication, reasoning that induction of hepatic microsomal enzymes by the drug would result in more rapid catabolism of vitamin D metabolites.¹ The treatment corrected the hypercalcaemia, and the raised serum total 25-hydroxyvitamin D concentration fell with induction of the enzymes, as indicated by a rise in γ -glutamyltransferase activity, but rose again when induction was stopped. Lukaszewicz *et al* successfully treated vitamin D₃ intoxication in a 7 month old boy using phenobarbitone and phenytoin to induce hepatic microsomal enzymes.² We report further analyses of the vitamin D metabolites in Iqbal and Taylor's patient.¹

Case report

The patient was a 77 year old woman who presented with confusion and had been taking 150 000 IU vitamin D₂ daily.¹ Investigations showed hypercalcaemia (3.52 mmol/l) with impaired renal function (plasma creatinine concentration 229 μ mol/l). Prednisolone 15 mg thrice daily failed to restore normocalcaemia and was withdrawn after 10 days. The plasma calcium concentration remained increased for 14 days, and glutethimide 500 mg at night was started.

Plasma concentrations of calcium (corrected for albumin binding) and γ -glutamyltransferase activity were measured by automated methods. The reference ranges were: calcium 2.2-2.7 mmol/l and γ -glutamyltransferase 0-65 U/l. To estimate the concentrations of metabolites of vitamin D serum was extracted by C18 Sep-paks; 1,25-dihydroxyvitamins D₂ and D₃ were measured by radioimmunoassay after separation by straight phase high performance liquid chromatography and the 25-hydroxy derivatives were measured by competitive binding assay after isolation by both straight and reverse phase high performance liquid chromatography.³ The reference ranges were: 25-hydroxyvitamin D₂ <12.5 nmol/l; 25-hydroxyvitamin D₃ 8-100 nmol/l; 1,25 dihydroxyvitamin D₂ <10 pmol/l; and 1,25-dihydroxyvitamin D₃ 50-156 pmol/l.

Hypercalcaemia was associated with raised serum concentrations of total 25-hydroxyvitamin D (1050 nmol/l) and total 1,25-dihydroxyvitamin D (260 pmol/l). Separate measurements of the metabolites of vitamin D₂ and vitamin D₃ showed that those of vitamin D₂ predominated (figure), reflecting the previous ingestion of excessive amounts of vitamin D₂. Eight days after administration of glutethimide plasma γ -glutamyltransferase activity rose above the upper limit of normal, peaking at 90 U/l on days 18-22. The plasma calcium concentration fell to within the normal range on day 13. The serum concentration of total 1,25-dihydroxyvitamin D began to fall within four days, and after eight days it was near the lower limit of the reference range, at 70 pmol/l. The serum concentration of total 25-hydroxyvitamin D did not change appreciably until hepatic enzymes were induced; thereafter it fell gradually. Although the 25-hydroxyvitamin D concentration remained high, the concentration of 1,25-dihydroxyvitamin D did not rise again but remained within the lower part of the normal range. The patient remained normocalcaemic,



Plasma concentrations of metabolites of vitamin D and plasma calcium concentration in patient with hypercalcaemia caused by vitamin D₂ intoxication who was treated with glutethimide. Hatched areas represent normal ranges; abscissa is marked in intervals of four days

and her renal function and confused state improved considerably.

Comment

Our results show that glutethimide causes supra-normal concentrations of 1,25-dihydroxyvitamin D to fall rapidly, with correction of hypercalcaemia and symptomatic improvement.¹ Because glutethimide induced synthesis of hepatic microsomal enzymes, as do the anticonvulsant drugs phenobarbitone and phenytoin, Iqbal and Taylor previously concluded that its hypocalcaemic effect was mediated through changes in the hepatic metabolism of vitamin D.¹ In vitro studies have shown, however, that glutethimide may act directly on renal 25-hydroxyvitamin D-1-hydroxylase by inhibiting its cytochrome P 450 component.⁴ Our results suggest that, although enhanced catabolism of 1,25-dihydroxyvitamin D cannot be excluded, an additional effect of glutethimide is to suppress the renal 1-hydroxylase enzyme; in this way it acts similarly to glucocorticoids.⁵

Glutethimide is no longer available in Great Britain, but in countries where it is available its use should be considered in vitamin D intoxication whenever glucocorticoids are ineffective or undesirable—for example, when there is congestive cardiac failure or renal failure.

Information about the availability of glutethimide may be obtained from Rorer Health Care Ltd, St Leonards House, St Leonards Road, Eastbourne BN21 3YG.

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Mortality from coronary heart disease in Asian communities in London

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In England and Wales in 1970-2 mortality from coronary heart disease was 20% higher in men and women who had been born in south Asia than in the general population.¹ Asian communities in Britain differ in religious, cultural, geographic, and genetic backgrounds; this diversity is similar to the differences among European populations with differing rates of coronary heart disease. In seeking causes of the high mortality from coronary heart disease in Asians rates for different groups must be established. Analysis of surnames on death certificates suggests that high rates are shared by Gujaratis, Punjabis, southerners, and Moslems, but this method has limitations.²

We examined the pattern of mortality in different ethnic groups originating from south Asia by using districts of residence to distinguish communities in which one group predominated; five London boroughs were chosen on this basis. In 1982 a survey in Brent and Harrow showed that 77% of Asians aged over 25 spoke Gujarati.³ In a 1985 survey of schoolchildren in Ealing Punjabi speakers accounted for 68% of those who spoke an Asian language at home; many of the 17% who spoke Hindi or Urdu also originated from the region that corresponded to Punjab before partition.⁴ Data from the 1981 census show that in Tower Hamlets 80% of the population born in south Asia and aged 20 and over were born in Bangladesh, and in Waltham Forest 56% were born in Pakistan. Mortality among Asians in these boroughs was therefore used as an indicator of mortality in Gujaratis, Punjabis, Bangladeshis, and to some extent Pakistanis.

Methods and results

Tables of deaths by underlying cause (International Classification of Disease 410-414 versus all other) and population figures from the 1981 census were obtained from the Office of Population Censuses and Surveys. Residents born in India, Pakistan, Bangladesh, and Sri Lanka were grouped as Asian; for Brent and Harrow residents born in east Africa were also included in this category. Standardised mortality ratios were calculated for Asians in each borough using the rates for that

borough as the standard and also, to facilitate direct comparison, using the rates for England and Wales in 1981 (table). Standardised proportional mortality ratios compare the observed and expected frequencies with which coronary heart disease is given as the underlying cause on death certificates; they do not depend on census data, and they measure the extent to which excess mortality is specific to a particular disease. Ratios for Asian women in Tower Hamlets and Waltham Forest were based on only a few deaths.

Comment

National data for mortality by country of birth in 1979-83 are not yet available but, unless the Asian populations that we studied are unrepresentative, mortality from coronary heart disease among Asians in England and Wales has increased by about 25% since 1970-2. The diminished effects of selection for fitness at migration may account for some of this increase. The economic state of Asian populations in London varies from the comparative affluence of Gujaratis in Brent and Harrow to the deprivation experienced by Bangladeshis in Tower Hamlets. Smoking rates range from very low in Gujarati women in Brent and Harrow³ to high in Bangladeshi men in Tower Hamlets.⁵ Most Asians in Brent and Harrow are vegetarian³ whereas the Moslem communities of Tower Hamlets and Waltham Forest are generally not. It is therefore striking that Asian men and women in each borough share a mortality from coronary heart disease 50% higher than the national average. Any general explanation of the high rates of coronary heart disease in south Asians overseas must invoke some factor that is common to the diverse communities that make up the Asian population in Britain.

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Mortality from coronary heart disease among Asians aged 20-64 in different London boroughs during 1979-83

London borough (predominant Asian ethnic group)	No of deaths	Standardised to average (100%) for each borough			Standardised to average (100%) for England and Wales	
		Standardised mortality ratio	95% Confidence interval	Proportional mortality ratio	Standardised mortality ratio	95% Confidence interval
Men						
Brent and Harrow (Gujarati)	177	163	138 to 187	146	160	136 to 183
Ealing (Punjabi)	118	136	111 to 161	122	147	120 to 173
Tower Hamlets (Bangladeshi)	49	118	85 to 151	132	141	102 to 180
Waltham Forest (Pakistani)	36	180	121 to 239	121	156	105 to 207
Women						
Brent and Harrow (Gujarati)	33	157	103 to 211	145	160	105 to 215
Ealing (Punjabi)	30	173	111 to 235	158	206	132 to 280
Tower Hamlets (Bangladeshi)	2	106*		136*	108*	
Waltham Forest (Pakistani)	7	318*		268*	217*	

*Ratio calculated from small numbers.